

The Great Chronic Idiopathic Urticaria Raft
Debate: After
Antihistamines, What's Best For Next In Line
Treatment:
Hydroxychloroquine and Dapsone


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Disclosures

- Research Grants
 - NIH, Vanberg Family Fund
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 - Merck, Astra Zeneca, Genentech
- Organizations:
 - Joint Task Force on Practice Parameters


Objective

- Be able to discuss the role of dapsone and hydroxychloroquine in the management of refractory CIU



Rationale for Alternative Agents in Chronic Urticaria

- While most urticaria is antihistamine responsive, not all patients have adequate control with antihistamine therapy at any dose
- Glucocorticoids** while typically effective, **have predictable and nearly universal toxicity for treatment of chronic urticaria**
- Alternative Agents
 - Immunomodulatory
 - Immunosuppressant
 - Other



Alternative Agents for CU

Leukotriene Modifiers	Methotrexate
Calcineurin Inhibitors	IVIG
Mycophenolate	Calcium channel blockers
Dapsone	Anticoagulants
Sulfasalazine	Cyclophosphamide
Colchicine	Gold
Hydroxychloroquine	Phototherapy
COX-2 inhibitors	Plasmapheresis
Androgens	
Omalizumab	

Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1


Matt Morgan, MD,*† and David A. Khan, MD*

Morgan M, Khan DA. Ann Allergy Asthma Immunol. 2008;100:403-412.

Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2

Matt Morgan, MD,*† and David A. Khan, MD*


Morgan M, Khan DA. Ann Allergy Asthma Immunol. 2008;100:517-26.



Category of Evidence

- Ia:** evidence for meta-analysis of randomized controlled trials
- Ib:** evidence from at least one randomized controlled trial
- IIa:** evidence from at least one controlled study without randomization
- IIb:** evidence from at least one other type of quasi-experimental study
- III :** evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
- IV :** evidence from expert committee reports or opinions or clinical experience of respected authorities, or both


Shekelle PG et al., BMJ 1999;318:593-6.



Second-Line Alternative Therapies for Chronic Urticaria


Drug	Level of Evidence
Leukotriene Modifiers	Ib
Dapsone	IIb
Sulfasalazine	III
Hydroxychloroquine	Ib
Colchicine	III
Calcineurin Inhibitors	Ib
Mycophenolate	IIb
Omalizumab	III

Khan DA. Allergy Asthma Proc 2008;29:439 -446.




Alternative Therapies in CIU: Factors in Choosing an Agent

- Safety
- Accessibility
- Ease of use
- Cost
- Efficacy
- Onset of action
- Potential for disease remission



Dapsone

- Early reports of efficacy were in patients with urticarial vasculitis
 - Matthews CN et al. Br J Dermatol 1978; 99: 455–7.
 - Highet AS. Br J Dermatol 1980; 102: 358–60.
 - Ruzicka T et al. Dermatologica 1981; 162: 203–5.
- Mechanisms of action
 - interference with release or function of lysosomal enzymes and myeloperoxidase generation of toxic halides
 - disruption of integrin-mediated neutrophil adhesiveness
 - inhibition of prostaglandin and leukotriene activity




Dapsone

- 5 pts with delayed pressure urticaria treated with response to dapsone 50 mg/d to qod
 - 3/5 complete remission off dapsone
 - Dayani A et al. J Dermatolog Treat 1992; 3: 61–2.
- Few reports in CIU
- Our experience >60% have improvement
 - Some with remission

Delayed pressure urticaria – Dapsone heading for first-line therapy?

Sonja Alexandra Grundmann, Sabine Kiefer, Thomas Anton Luger, Randolph Brehler
Clinic and Polyclinic for Dermatological Diseases, Münster University Hospital, Germany

Grundmann SA et al. JDDG 2011;9:1-5.



Dapsone in Delayed Pressure Urticaria

- Retrospective study of 31 patients with delayed pressure urticaria
 - Confirmed with standardized pressure challenge tests
- All patients failed treatment with high dose antihistamines and montelukast
- Baseline G-6PD and Met-Hb levels

Grundmann SA et al. JDDG 2011;9:1-5.





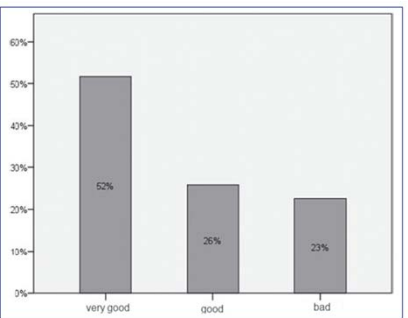
Table 1: Dosage of dapsone therapy.

1 week	25 mg dapsone + 1 g vitamin C
2 weeks	50 mg dapsone + 1 g vitamin C
3 weeks	100 mg dapsone + 1 g vitamin C
> 4 weeks	150 mg dapsone + 1 g vitamin C

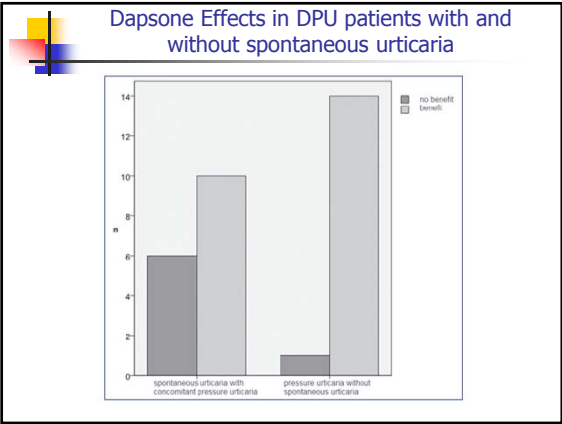
Grundmann SA et al. JDDG 2011;9:1-5.



Response to dapsone



Response Category	Percentage
very good	52%
good	26%
bad	23%



Duration of Treatment and DPU and Effect on Dapsone Response

Table 6: Influence of length of dapsone use and duration of pressure urticaria on therapeutic benefit.


benefit	sum	therapy with dapsone			duration of pressure urticaria			
		<= 7 weeks	8-12 weeks	>12 weeks	< 1 year	1-3 years	3-6 years	> 6 years
good or very good	24 (77 %)	6 (55 %)	10 (91 %)	8 (89 %)	13 (93 %)	5 (83 %)	2 (33 %)	4 (80 %)
poor	7 (23 %)	5 (45 %)	11 (9 %)	1 (11 %)	1 (7 %)	1 (17 %)	4 (67 %)	1 (20 %)
sum	31 (100 %)	11 (100 %)	11 (100 %)	9(100 %)	14 (100 %)	6 (100 %)	6 (100 %)	5 (100 %)

Grundmann SA et al. JDDG 2011;9:1-5.

Author's Conclusions

- Although the mechanisms of action of sulfone derivatives in pressure urticaria are uncertain, we believe that with adequate monitoring the **risk-to-benefit** ratio of dapsone therapy in treatment-resistant forms **is so impressive that it warrants early treatment initiation.**


Grundmann SA et al. JDDG 2011;9:1-5.



Low Dose Dapsone in CU

- Small open study in 11 CU patients (3 with DPU)
- Treated with dapsone 25 mg daily
 - Dose increased to 50 mg daily if no response after 4 weeks
- 9/11 had complete response to dapsone 25 mg/d
- 1/11 had complete response to dapsone 50 mg/d


Cassano et al. Acta Derm Venereol 2005;85:254-5.



Dapsone + Antihistamine


- 65 CIU pts randomized to 3 months of open label:
 - Dapsone + desloratadine
 - Desloratadine
- Combination of dapsone plus desloratadine yielded statistically significant improvements in urticaria activity and VAS scores vs. desloratadine alone

Engin B et al. J Eur Acad Dermatol Venereol. 2008 Apr;22(4):481-6




Dapsone

- Evidence: IIb
- Advantages
 - Inexpensive
 - Usually well-tolerated
 - Mild anemia expected (Hgb ↓ by 10-20%)
 - Neuropathy uncommon but often irreversible
 - Methemoglobinemia/hepatitis rare
 - May induce remission
- Requires regular monitoring of CBC



Dapsone

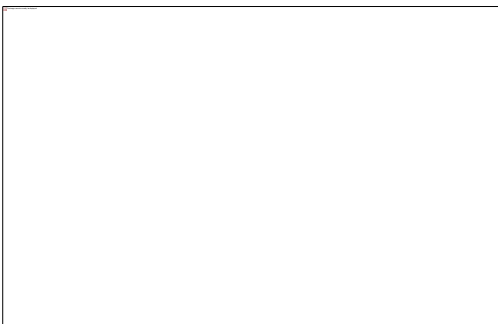
- Dose
 - 50-100 mg/d
- Monitoring
 - G6PD level prior to starting
 - CBC
 - 1-2 weeks after initiation
 - monthly for 3-6 months then periodically
 - LFT's periodically



Hydroxychloroquine


- Mechanism of action
 - Suppression of T-cell activation
 - Disruption of antigen processing
- 18 pts with CIU randomized to hydroxychloroquine vs. placebo along with H1, H2 and corticosteroid therapy
- After 12 weeks, QOL and itch was improved with trends of improvement for urticaria score and medication requirement
- Minimal correlation with ASST and autoimmune markers

Reeves GEM et al. Int Med J 2004;34:182-6.




GSS: itch severity US: urticaria score
LAMY & SF-12: general QOL

Reeves GEM et al. Int Med J 2004;34:182-6.



Hydroxychloroquine

- Evidence: Ib
- Dosing
 - 200 mg qd to bid
- Advantages
 - Safe
 - Risk of retinopathy very rare and related to dose and duration
 - Inexpensive
- Disadvantages
 - Slow onset of effect
 - 12 week trial typically recommended




American Academy of Ophthalmology Update

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

Michael F. Marmor, MD,¹ Ulrich Kellner, MD,² Timothy Y. Y. Lai, MD,³ Jonathan S. Lyons, MD,⁴
William F. Miesler, MD,⁵ for the American Academy of Ophthalmology

Baseline examination within 1st year of use
Annual screening after 5 years of use

Ophthalmology 2011;118:415-422.




Recommendations for Hydroxychloroquine Retinopathy Screening

Risk Factors for Hydroxychloroquine Retinopathy	
Duration of use	> 5 yrs
Cumulative dose	>1000 gms
Daily dose	> 400 mg/d
Age	Elderly
Systemic disease	Kidney or liver dysfunction
Ocular disease	Retinal disease or maculopathy

Annual screening recommended at initiation of drug if above risk factor(s) present


Ophthalmology 2011;118:415-422.



**Factors in Choosing an Alternative Agent:
How do Dapsone and Hydroxychloroquine stack up?**

	Dapsone	Hydroxychloroquine
Safety	++	+++
Accessibility	+++	+++
Ease of Use	++	+++
Cost	+++	+++
Efficacy	++	++
Onset of action	++	+
Potential for disease remission	+++	++

+++ : very favorable
++ : favorable
+ : slightly favorable
- : not favorable



**After
Antihistamines, What's Best For
Next In Line Treatment?**

Clearly the answer is dapsone or
hydroxychloroquine !
